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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PATEL, SUDHAKER B	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 07/10/2003

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/046,526	CHEN ET AL.	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication appears on the cov r sheet with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *4 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,10-12 and 14-17* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on ____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' communication paper # 8 dated 6/11/03 is acknowledged.

Election/Restrictions

1. Because applicants did not distinctly and specifically point out the supposed errors in the restriction/election requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Applicants have elected invention of Group II, and species of generic Formula (I') of claim 1, namely, compound of Example 65 recited in page 200 lines 17-24 (= 2-(4-fluoro-benzylamino)-N-{4-[4-methyl-1-(1-methyl-piperidine-4-yl)-ethyl]-phenyl}-nicotinic acid amide), claims (in part) 1-17, drawn to compounds, compositions, method of use, for the generic Formula (I') wherein A = pyridine.

Applicants are reminded of the election of species guidelines provided in MPEP 803.02, which are followed for the examination.

The elected species of compound of Example 65 as stated earlier has following meanings for variables in the generic Formula (I') of claim 1:

X	= 3-position of pyridine occupied by -CO-NH-;
A	= 3-pyridinyl with compared to –CONH- variable(= nicotinic acid core) ;
R2	= Substituted phenyl;
Y	= -NHCH2-;
R3	= Halo-substituted phenyl ;
R1	= H;

Initial search with above definitions of the variables for the species did not reveal prior art(s). Therefore, the search was expanded to Y = -NHSO2-, and the meanings of other variables were as stated above i.e.

X	= 3-position of pyridine occupied by -CO-NH-;
A	= 3-pyridinyl with compared to –CONH- variable(= nicotinic acid core) ;
R2	= Substituted phenyl;
Y	= -NH-SO2--;
R3	= substituted phenyl ;
R1	= H;

Further search with above meanings of variables revealed prior art(s).See rejections bellow.

Therefore, as per guidelines, the search was limited to meanings of variables as stated above only.

All other definitions of variables than stated above are excluded from further consideration. 37 CFR 1.142(b).

Since claims 1-3,5-8,10-17 link with non-elected subject matter they will be examined bearing in mind the subject matter and invention of Group II as recited above only. Additionally Claims 4, 9 are withdrawn from further consideration by examiner as they constitute non-elected subject matter. 37 CFR 1.142(b).

This application has been found to contain more than one invention. Therefore, restriction/election has been considered proper, and is now made FINAL.

First action on merits follows.

Information Disclosure Statement

2. The information disclosure statement (IDS) paper # 5 & 6 submitted on 6/17/02 & 11/27/02 respectively are acknowledged, and the same been considered by the

examiner. Signed copies of PTO Form 1449 are enclosed with this communication for applicants' record.

Claim Objections

3. Claim 13 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim 12 is dependent on claims 1-10. See MPEP § 608.01(n). Accordingly, the claim 13 has not been further treated on the merits.

4. ***Double Patenting***

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1-3,5-8,10-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 10197960 filed 7/17/02. Although the conflicting claims are not identical, they are not patentably distinct from each other because subject matter related to compounds, composition, method of use/utility of ref. ' 960 claims 1-20 are also recited by the instant claims.

3. The variables of generic Formula (I') of instant application encompass ref/ '960 compounds with following meanings:

X	= 3-position of pyridine occupied by -CO-NH-;
A	= 3-pyridinyl with compared to –CONH- variable(= nicotinic acid core) ;
R2	= phenyl;
Y	= -NHCH2-;
R3	= R8-substituted phenyl ;
R1	= H;

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3,5-8,10-12,14-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Schindler et al (W) 2000002851 dated 1/20/2000, also cited as DE 19830430 dated 1/13/2000, and as Chemical Abstract DN 132:93104).

The ref. '851 teaches making of 3-pyridinecarboxamide derivatives which are encompassed by the Formula (I') of instant claims in the following manner:

X	= 3-position of pyridine occupied by -CO-NH-;
A	= 3-pyridinyl with compared to –CONH- variable(= nicotinic acid core) ;
R2	= Substituted phenyl;
Y	= -NH-SO2-;
R3	= substituted phenyl ;
R1	= H.

Following ref. '851 compounds having:
CAS RN # 254877-06-0(3-pyridinecarboxamide, N-[[4-(aminocarbonyl)-1-piperidinyl]sulfonyl]phenyl]-2-[[(4-chlorophenyl)sulfonyl]amino-);
CAS RN # 254877-07-1(3-pyridinecarboxamide, 2-[[4-(chlorophenyl)-sulfonyl] amino]-N-[4-(1-piperidinylsulfonyl]phenyl]-;
CAS RN # 254975-95-6(3-pyridinecarboxamide, 2-[[4-(chlorophenyl)-sulfonyl] amino]-N-[4[[(2R,6S)-2,6,-dimethyl-4-morpholinyl]sulfonyl]phenyl]-.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3,5-8,10-12,14-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply.

(A). Claims 1-3,5,7,8,10 recite(where applicable): " a compound of Formula I' and pharmaceutically acceptable (isomers) derivatives thereof;" It is not very clear as to what is exactly being claimed. The recited words include other compounds, which are not included in the specification. Correction to: "a compound of Formula I' or its pharmaceutically acceptable (isomers) or salts thereof;" is required.

(B). Claims 12,14,16,17 which are related to method of treating recite: " an effective amount of a compound". Correction to: " therapeutically effective amount of a compound" is required.

(C). Claim 11 is rejected because it is dependent on rejected claims.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12,14,16,17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for arthritis, does not reasonably provide enablement for cancer and other diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The method of use claims recites generic diseases, e.g. cancer, angiogenesis, KDR-related disorders, treatment of proliferation and diseases yet to be discovered.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: **(1).** *The nature of invention;* **(2).** *the state of prior art ;* **(3).** *the predictability or lack thereof in the art;* **(4).** *the amount of direction or guidance present;* **(5).** *the presence or absence of working examples;* **(6).** *the breadth of the claims, and* **(7).** *the quantity of experimentation needed.*

Discussion about cancer(s):

For example, the claims set forth not only the treatment of a specific cancer, but also prevention of cancers and other diseases, generally. However, there never has been a compound capable of treating various types of cancers. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancers and pain as recited earlier, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective anti-cancer agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologist today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. This is only for one of the many disorders as claimed herein.

Following references are quoted to show the state of art:

□ ***Cecil Textbook of Medicine*** states that: " each specific type of cancer has unique biological and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see In re Butting, 163, USPQ 689 (CCPA 1969), wherein "evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers".

Structure-Based Design of Novel Anticancer Agent:

Uckun et al(see Current Cancer Drug Targets, 1,59-71(2001) concludes in pages 66-67 that : " WHI-P131, which inhibits JAK3 but does not inhibit JAK1, JAK2, SYK,BTK,LYN or IRP even at concentrations as high as 350uM is undergoing further studies to evaluate its potential use as a new anti leukemic agent(in children).

Agents that inhibit epidermal growth factor receptor(EGFR) may be useful for treatment of breast cancer.

Tubulin modulating agents, which are of natural as well as synthetic origin, can be used as effective anticancer agents for treating breast cancer.

COBRA compounds caused destruction of microtubule organization and apoptosis. Like other microtubule-interfering agents, COBRA compounds activated the proapoptotic c-Jun N-terminal kinase (JNK) signal transduction pathway, as evidenced by rapid induction of c-jun expression".

Specification on pages 216-222 recite methods of assay and test carried out for the selected examples of present invention.

Some of the results could be summarized as:

- Note, there are no comparative test/assay results for the elected species.
- The HUVEC proliferation assay for the selected compounds are presented as: "inhibited VEGF-stimulated HUV EC proliferationat a level below 50nM" This value represents a range 0-50 nM.
- The rat micropocket assay(s) is recited on page 221, lines 7-9 as: " compounds of the present invention will inhibit angiogenesis as a dose of less than 50 mg/kg/day".
- The Tumor model assay(s) is recited as: " Compounds of present invention are active at doses less that 150 mpk".
- There is no test/assay for art recognized ref. Compound for comparison.

These results are not sufficient to support the methods of use claims not claiming treating of a specific disease of an organ but to treating cancer, and other diseases as

recited herein. Therefore, these results will help as a preliminary guideline for screening the compounds only.

Statements of utility, which relate to or imply to treatment of a disease are subject to closer scrutiny. Ex parte Moore et al(POBA 1960) 128 USPQ 8. Claims do not meet the Utility Guidelines. The claims do not qualify as one utility statement, and are not believable on their face. Claims will require too much experimentation to determine what patient dosage relationship would produce what results. It is not believable on its face that any one compound would have all of those utilities. In re Hozumi, 226 USPQ 353.

Evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of claims directed to a method of treating 7 types of cancer with member of a class of several compounds. In re Buting, (CCPA 1969) 418 F2d 540, 163 USPQ 689.

The quantity of experimentation need would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skilled in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims involving use of compounds, their compositions.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that

achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 15 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a step/process asserted utility or a well-established utility.

The claim recites the use of a compound of any of claims 1-10 in a method of therapeutic treatment for human as well as animal body. The method of treatment does not indicate the steps involved:

- for treating the people;
- for identifying the people/ animal who will require the said generic treatment,

and the claim does not exactly say about the disease to be treated.

Claim 15 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a step/process asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone

number is 703 308 4709. The examiner can normally be reached on 6:30 to 5:00 pm (Monday-Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on 703 308 4716 or Sr. Examiner Mr. Richard Raymond at (703) 308 4523.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.

SP/June 20, 2003

MUKUND J. SHAH
SUPERVISORY PATENT EXAMINER
GROUP 1600